

CLAIMS:

1. A method of detecting an interaction between a bait polypeptide and a prey polypeptide comprising:

5 introducing a first nucleic acid encoding a first hybrid protein into a host cell, the first nucleic acid having a first exogenously activatable promoter, and the first hybrid protein having a DNA binding region and the bait polypeptide;

10 introducing a second nucleic acid encoding a second hybrid protein into the host cell, the second nucleic acid having a second exogenously activatable promoter different from the first exogenously activatable promoter, and the second hybrid protein having a transcriptional activation region and the prey polypeptide;

15 activating the first and second promoters using first and second exogenous activators to induce expression of the first and second hybrid proteins; and

20 detecting an interaction between the bait polypeptide and the prey polypeptide by activation of a detectable reporter gene in the host cell, wherein the DNA binding region binds near the reporter gene and the transcriptional activation region activates transcription of the reporter gene when brought into proximity to the reporter gene by an interaction between the bait polypeptide and the prey polypeptide;

25 wherein sensitivity of detecting an interaction may be continuously adjusted by altering the relative or absolute amount of at least one of the first or second hybrid proteins in the host cell and wherein amounts of the first and second hybrid proteins in the host cell are independent of one another.

2. The method of Claim 1, further comprising continuously adjusting the amount of the first hybrid protein in the host cell through activation of the first 5 exogenous promoter.

3. The method of Claim 1, further comprising continuously adjusting the amount of the second hybrid protein in the host cell through activation of the second 10 exogenous promoter.

4. The method of Claim 1, wherein the first nucleic acid further comprises a plurality of exogenous promoters operable to induce expression of the first hybrid protein in 15 the host cell over a wider continuous range of amounts than the range obtainable using only one of the plurality of exogenous promoters.

5. The method of Claim 1, wherein the second nucleic 20 acid further comprises a plurality of exogenous promoters operable to induce expression of the second hybrid protein in the host cell over a wider continuous range of amounts than the range obtainable using only one of the plurality of exogenous promoters.

25 6. The method of Claim 1, further comprising detecting a detectable reporter protein produced by activation of the detectable reporter gene.

30 7. The method of Claim 1, wherein sensitivity of detecting an interaction may be continuously adjusted on a dose-responsive basis.

8. The method of Claim 1, further comprising interfering with activation of at least one of the first or second exogenously activatable promoters by providing a 5 modulatory agent to the host cell.

9. The method of Claim 1, wherein at least one of the first or second exogenous activators comprises a natural or synthetic, metabolically active or inactive steroid, steroid 10 analogue or steroid mimic.

10. The method of Claim 1, further comprising at least one of the first or second exogenous activators selected from the group consisting of: cortisol, cortisone, 15 hydrocortisone, mineralcorticoids and mineralcorticoid analogues, dexamethasone estrogen, estradiol, estrone, progesterone, androgens, ecdysone, retinoid, steroids complementary to orphan receptors, other agent operable to interact with steroid responsive elements, and any 20 combinations thereof.

11. The method of Claim 1, wherein at least one of the first or second exogenous activators comprises a membrane-active agent or analog thereof selected from the group 25 consisting of: ionophores, anesthetic agents, detergents, amphoteric agents, hydrophobic agents, lipid-active agents, solvents, transmembrane signaling agents, intramembrane signaling agents, farnesylating agents, and any combinations thereof.

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12. The method of Claim 1, wherein at least one of the first or second exogenous activators comprises a small

molecular pharmaceutical agent selected from the group consisting of: antimicrobial agents, anti-tumor agents, nucleic acid-binding agents, cytoskeletal active agents, chelators, inducers, co-repressors, agents affecting 5 intracellular trafficking, localization, protection and degradation of exogenous or endogenous mediators, hormones, and any combinations thereof.

13. The method of Claim 1, wherein at least one of the 10 first or second exogenous activators comprises a biomolecule or natural or synthetic biopharmaceutical selected from the group consisting of: growth factors, cytokines, hormones, their cellular receptors, fragments thereof, mimics thereof, and any combination thereof.

14. A method of detecting an interaction between a bait polypeptide and a prey polypeptide comprising:

introducing a first nucleic acid encoding a first hybrid protein into a host cell, the first nucleic acid having an estrogen-sensitive promoter, and the first hybrid protein having a GAL4 binding domain and the bait polypeptide;

introducing a second nucleic acid encoding a second hybrid protein into the host cell, the second nucleic acid having a glucocorticoid-sensitive promoter, and the second hybrid protein having a GAL4 transcriptional activation domain and the prey polypeptide;

activating the promoters to induce expression of the first and second hybrid proteins; and

detecting an interaction between the bait polypeptide and the prey polypeptide by activation of a UAS_g-LacZ reporter gene in the host cell;

wherein sensitivity of detecting an interaction may be continuously adjusted by altering the relative or absolute amount of at least one of the first or second hybrid proteins in the host cell and wherein amounts of the first and second hybrid proteins in the host cell are independent of one another.

15. The method of Claim 14, wherein activating the promoters further comprises supplying estrogen or an estrogen analogue and a glucocorticoid or a glucorticoid analog to the host cell.

16. The method of Claim 14, wherein sensitivity of detecting an interaction may be continuously adjusted by

altering the amount of estrogen or an estrogen analogue supplied to the host cell.

17. The method of Claim 14, wherein sensitivity of
5 detecting an interaction may be continuously adjusted by
altering the amount of glucocorticoid or a glucocorticoid
analogue supplied to the host cell.

10 18. The method of Claim 14, further comprising
continuously adjusting the amount of the first hybrid
protein in the host cell through activation of the estrogen-
sensitive promoter.

15 19. The method of Claim 14, further comprising
continuously adjusting the amount of the second hybrid
protein in the host cell through activation of the
glucocorticoid-sensitive promoter.

20 20. The method of Claim 14, further comprising
detecting LacZ produced by activation of UAS_g-LacZ reporter
gene.

25 21. The method of Claim 20, further comprising
detecting LacZ using colorimetric analysis.